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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,597	03/23/2001	Maurice J. Wolin	PP01658.002(035784/209107	7188

826 7590 05/03/2004

ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
HUFF, SHEELA JITENDRA	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,597	WOLIN ET AL.	
	Examiner	Art Unit	
	Sheela J Huff	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed 4/1/04 has been considered. Applicant's arguments are deemed to be persuasive-in-part.

Claims 1-19 have been cancelled.

Claims 20-44 have been added and are currently pending.

Priority

The provisional application 60/192047 has been examined by the Examiner. Applicant has priority to 3/24/00.

Withdrawn Rejections

The rejection of claims 1-7, 13-15 and 17 under 35 U.S.C. 102(a) as being anticipated by Freidberg et al Blood (11/16/00) Vol. 96(11) part 1 pp. 730a Abstract only is withdrawn in view of the priority to the provisional application.

The rejection of claims 1-7 and 13-16 under 35 U.S.C. 102(b) as being anticipated by Yirinec et al. Blood vol. 94 p. 270b Abstract 4420 is withdrawn in view of the priority to the provisional application and in view of the Katz Declaration.

The rejection of claims 1, 3 and 4 under 35 U.S.C. 102(b) as being anticipated Hooijberg et al Cancer Research vol. 55 p. 2627 (1995) is withdrawn in view of applicant's amendment.

The rejection of claims 1-19 under 35 U.S.C. 103(a) as being unpatentable over Freidberg et al Blood (11/16/00) Vol. 96(11) part 1 pp. 730a Abstract only, in view of

applicant's admission on page 18, line 11 to page 21 is withdrawn in view the newly established priority.

The rejection of claims 1-19 under 35 U.S.C. 103 as being obvious over Yirinec et al. Blood vol. 94 p. 270b Abstract 4420, in view of applicant's admission on page 18, line 11 to page 21 in view of the priority to the provisional application and in view of the Katz Declaration.

The rejection of claims 1, 3-5 and 7-19 under 35 U.S.C. 103 as being obvious over Hooijberg et al Cancer Research vol. 55 p. 2627 (1995), in view of applicant's admission on page 4, line 13 and page 18, line 11 to page 21 in view of applicant's amendment.

The rejection of claims 1-19 under 35 U.S.C. 103(a) as being unpatentable over WO 00/09160 or US 6455043 (priority to 8/11/98) in view of), in view of applicant's admission on page 18, line 11 to page 21 is withdrawn and re-written in view of applicant's amendment.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 36-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

In claim 36, applicant claims that the IL-2 or variant is administered three times per week. For support for this applicant points to original claim 18. Claim 18 only refers to daily administration of IL-2. Thus, the newly added limitation "three times per week" is new matter.

Claims 31-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 31, line 1 applicant states "said concurrent therapy". There is no proper antecedent basis for this terminology.

Claims 33 and 37 are confusing. In claim 33, applicant states that the does is administered daily for a period of 4 weeks. However, in claim 32 the IL-2 is administered only beginning on day 8. Does applicant 4 weeks after day 8? Or does applicant mean 4 weeks from the first day? If applicant means this then claim 33 does not further limit claim 32. Similar issue is found between claims 36 and 37.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/09160 or US 6455043 (priority to 8/11/98) in view of applicant's admission on page 18, line 11 to page 21.

The WO document is the WO of the patent 6455043.

Both references disclose a combined therapeutic regime for Non-Hodgkin's B cell lymphomas using anti-CD20 antibodies (specifically IDEC-C2B8) and cytokines (IL-2) (see abstract of both, col. 3, lines 11-35, col. 2, line 54-56, col. 13+ of patent and pages

5-6 and 25+ of the WO). The dose of IDEC-C2B8 used ranges from 125-375 mg/m2 (col. 8, line 60-64 of patent and page 16 of WO). The references also disclose that Phase I and Phase II studies are in progress to evaluate safety and to evaluate the "efficacy and the incidence of HACA formation in patients receiving low-dose IL-2 and Rituxan" (page 28, lines 9-11 of the WO). Thus, these references disclose the in vivo human use of a combination therapy.

The only difference between the instant application and the references is a showing of what dose of IL-2 was used and "variants" of IL-2.

On pages 18-21, applicant admits that functional variants of IL-2 are well known in the art (see specifically page 18, line 30 to page 19, line12). The variant of claims 28 and 42 is specifically disclosed at page 19, lines 6-8. On page 19 bottom to page 21, applicant admits that the stabilized forms of IL-2 are art known.

On pages 25-28 of the WO and columns 13-15 of the patent, the references disclose a variety of different low doses effective in treatment. These include 2 mIU/m2 (as disclosed by Lauria et al) or 0.45 mIU/m2 as disclose by Caligiuru et al (col. 14, line 27 and 48-50 of the patent). Thus the low doses disclosed in the reference read on applicant's low dose. Therefore, in view of effectiveness of the low doses, it would have been obvious to one of ordinary skill in the art to use the low doses mentioned by the reference in a combination treatment with the expected benefits of treating NHL. It also would have been obvious to one of ordinary skill in the art to optimize the treatment and dosages with the expected benefits of treating B-cell lymphoma. It also would have been obvious to use any known IL-2 variant or stabilized form of IL-2 in view of

applicant's admission that they are known in the art. The use of art known equivalents for the same purpose is obvious. The route of administration is within the purview of one skilled in the art unless criticality for the subcutaneous route can be shown.

Response to Applicant's arguments

Applicant argues that one "cannot predict what the combined effect of the two drugs will be". Applicant's arguments are moot in view of the on going Phase II trials.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheela J Huff whose telephone number is 571-272-

0834. The examiner can normally be reached on Tuesday 5:30am-11:30am and Fridays 6:00am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheela J Huff
Primary Examiner
Art Unit 1642

sjh